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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/011,910	02/17/98	ABRIGNANI S	0336.001

027476
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HM12/1024

EXAMINER	
BRUMBACK, B	
ART UNIT	**PAPER NUMBER**
1642	23

DATE MAILED: 10/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/011,910	Applicant(s) ABRIGNANI, SERGIO	
	Examiner Brenda G. Brumback	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,7-10 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,7-10 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This action is responsive to the amendment filed 08/06/2001. Claims 13 and 14 were canceled. Claims 3, 4, 10, and 17 were amended. Claims 2-4, 7-10, and 17 are pending and under examination.

Claim Rejections - 35 USC § 112

2. The rejection of claims 13 and 14 under 35 U.S.C., first paragraph, is now moot, as these claims have been canceled.

3. The rejection of claims 2-4, 7-10, 13, 14, and 17 under 35 U.S.C. 112, second paragraph, is withdrawn pursuant to applicant's amendment of claims 2-4, 7-10, and 17 and cancellation of claims 13 and 14.

NEW GROUNDS OF REJECTION

Specification

4. The disclosure is objected to because of the following informality: The page numbers of the Table of Contents (pages 12-13) should be deleted, as the pages numbers of the specification would not be retained in a printed patent.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claims 2-4, 7-10, and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a "written description" rejection.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the "written description" inquiry, is *whatever is now claimed*" (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., a protein having a molecular weight of about 24kd which specifically binds to the E2 protein of hepatitis C virus and functionally equivalent variants and fragments of the protein which bind the E2 protein of hepatitis C virus.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly & Co., 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *The reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species

encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention".

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* a 24kd protein which specifically binds the E2 protein of hepatitis C virus. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claims encompass numerous species that are not further described, *i.e.* functionally equivalent variants and fragments of the 24kd protein which specifically binds hepatitis C virus E2. There is substantial variability among the species. While the disclosure defines a functional variant as a chemical modification of the 24kd protein which may include one or more insertions, deletions, or replaced amino acids, there is no further description. There is neither a description of the amino acid sequence of the 24kd protein, nor of any functionally equivalent variants thereof.

Weighing all factors, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus which comprises a protein having a molecular weight of about 24kd that specifically binds to the E2 protein of hepatitis C virus and functionally equivalent variants and fragments of the protein. The specification does not "clearly

allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

6. Claims 2-4, 7-10, and 17 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for a protein having a molecular weight of about 24kd, does not reasonably provide enablement for functionally equivalent variants and fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150

(CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a process for the preparation of a protein having a molecular weight of about 24kd which specifically binds to the E2 protein of hepatitis C virus or a functionally equivalent variant or fragment thereof and to a diagnostic kit comprising the protein or functionally equivalent variant or fragment thereof. The specification defines a variant as a chemically modified 24kd protein which may include one or more insertions, deletions, or replaced amino acids.

The state of the prior art and the predictability or lack thereof in the art: Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can

be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

The amount of direction or guidance present and the presence or absence of working examples: The specification discloses isolation and characterization of a protein having a molecular weight of about 24kd which specifically binds the E2 protein of hepatitis C virus. The specification discloses and provides a working example for a process for preparing that protein. The disclosure does not disclose any functionally equivalent fragments or variants of the protein. While the specification teaches a variant as a chemical modification of the 24kd protein which may involve one or more insertions, deletions, or replacements of amino acids, it fails to teach the amino acid sequence of the 24kd protein and fails to provide any guidance as to which amino

acids could be substituted for or deleted without adversely affecting the binding of the E2 protein of hepatitis C virus.

The breadth of the claims and the quantity of experimentation needed: Because the claims encompass functionally equivalent variants and fragments of the 24kd protein, and because the specification fails to contain sufficient teachings to overcome the teachings of unpredictability found in the art regarding variants or proteins having amino acid changes, it would required undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

7. Claims 2-4, 7-10, and 17 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claimed invention is drawn to a process for the preparation of a protein having a molecular weight of about 24kd which specifically binds to the E2 protein of hepatitis C virus or a functionally equivalent variant or fragment thereof. While the specification defines a variant as a chemical modification of the 24kd protein which may involve one or more insertions, deletions, or replacements of amino acids (see page 3), it fails to teach the amino acid sequence of the 24kd protein. Absent such recitation, the metes and bounds of such amino acid insertions, deletions, and replacements cannot be determined and the claims are indefinite.

Claim Objections

8. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 2 is drawn to the protein or functionally equivalent variant or fragment thereof of claim 1, which is functionally unglycosylated. The disclosure teaches that the protein of claim 1 is inherently unglycosylated; thus, claim 2 does not further limit claim 1. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

Conclusion

9. No claims are allowed.

10. Due to the new grounds of rejection herein, this action is made nonfinal.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will

be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
October 22, 2001

Brenda Brumback,
Patent Examiner